

New Developments in Dry Powder Inhaler Technology

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Recent developments in the area of inhalation technology, stimulated primarily by the 'phase-out' of chlorofluorocarbon (CFC) propellants in pressurized inhalers under the terms of the Montreal Protocol (1) together with the desire to use the lungs as a portal to the systemic circulation (2), have resulted in the development of many innovative technology platforms. Dry powder inhalers (DPIs), in particular, have received considerable attention because of their propellant-free composition and the patient's inherent coordination with actuation. However, systemic pulmonary delivery of both small and macromolecules presents unique challenges. Efficient and reproducible drug deposition in the deep lung is essential for systemic delivery of expensive compounds with narrow therapeutic windows. Furthermore, the peptides and proteins intended for systemic delivery have distinctive physicochemical properties - these are high molecular weight, unstable compounds which require large 'lung-doses' in the order of 2 - 20 mg (2). Traditional powder aerosol formulations are inefficient with fine particle doses 20 - 30% of total emitted dose (3) and unreproducible (4). Coupled with regulatory requirements that inhaler systems meter and aerosolize micronized (usually < 5 µm) powders reproducibly (5), a myriad of novel inhaler devices have emerged together with the introduction of novel material processing techniques. The purpose of this review is to address novel devices and 'smart' particles and indicate the new directions the industry is following for conventional anti-asthma drugs and new macromolecules.

Novel Device Technology

Ideal dry powder inhaler (DPI) devices should seek to deliver drugs efficiently and reproducibly in addition to being both patient-friendly and cost-effective. Powder inhalers contain drug formulation pre-metered as capsules (unit-dose inhalers), blisters and cartridges (multi-unit dose inhalers), or alternatively as bulk material in a reservoir (multidose inhalers) (6-9). First generation powder inhalers - 'passive devices' - rely solely upon the patient's inspiration as the energy source for powder aerosolization and deaggregation. Second generation or 'active' powder inhalers utilize an additional energy source e.g. compressed air, a hammer, or a motorized propeller to aerosolize the powder formulation reducing patient-dependence

upon dispersion, and thus improving dosing reproducibility. However, these devices are highly complex, expensive and demand increased regulatory inspection. Consequently, such devices may be cost-prohibitive for asthma therapy and should be considered only for those compounds, which are intended for systemic administration.

There has been tremendous activity in the development of DPI devices over recent years with many innovative systems now at various stages of development (conceptual through to marketed products), which are summarized in Table 1. Specific information relating to individual powder inhaler design and operation is beyond the scope of the present article, and the reader is directed to the excellent reviews in this area (6-9).

Since the introduction of the first generation of passive unit dose DPIs - Fisons Spinhaler™ (10) and GSK Rotahaler™ (11) - powder inhalers have advanced with respect to both their complexity and performance. Whilst recent innovations in the area of DPI devices have focused primarily on the development of multiple dose systems, some companies have developed novel unit dose devices, for example Inhance™ Pulmonary Delivery System (38). This device utilizes compressed air to pre-aerosolize the formulation, independent of the patient's inspiratory effort, into a transparent holding chamber enabling patients to view the aerosol before inhalation (38). This device has been designed for the systemic delivery of insulin and other proteins.

The inherent advantages offered by multi-unit dose devices (pre-metered doses designed to provide the highly consistent dose metering demanded by regulatory standards (5)) have catalyzed perhaps the most aggressive research and development of all the powder systems. Marketed multi-unit dose devices include GSK Diskhaler™ and more recently Accuhaler™ (17, 18). Innovative multi-unit device systems, at various levels of development, include Spiros™ and Spiros™ S2 (20,39). Spiros™ DPI technology applies electro-mechanical energy (breath actuated battery operated propeller) to aerosolize and disperse powdered medication, rather than depending upon the patients inspiratory effort or propellants (39). Improved lung drug deposition is claimed since the patient can achieve efficient inhaler performance using a slow deep inspiration. Again, it is interesting to note that one supplier has introduced a second-generation device, which does not employ a motorized propeller, instead, free-floating beads within the

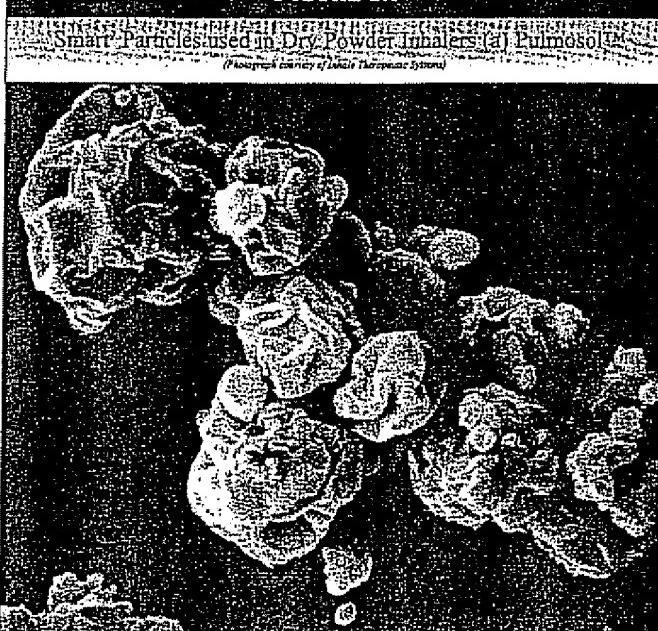
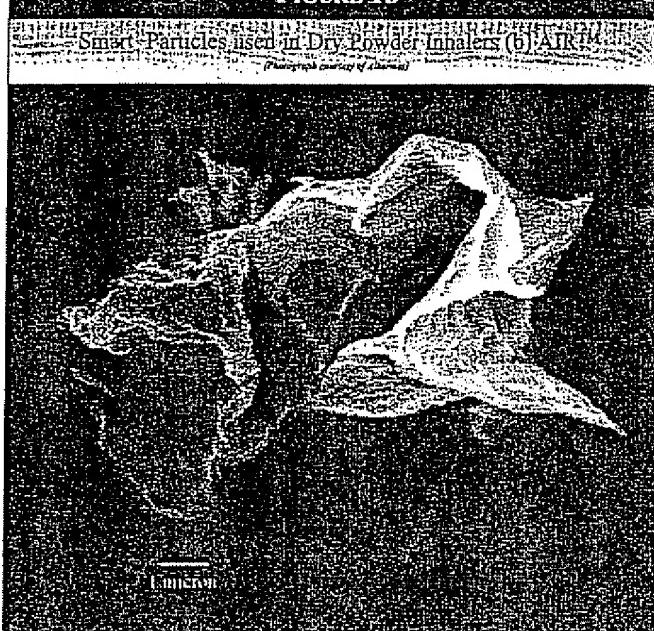
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device chamber create a powder dispersion. A further patent has been issued where dispersion is achieved using a turbine assembly to propel the motor, instead of batteries (26) – it would appear that perhaps the industry is returning towards efficient but inexpensive passive devices. Spiros' technologies, designed to aerosolize simple lactose carrier / milled drug formulations (without the need for sophisticated formulation technologies), were originally intended for small molecules but are now being developed for delivery of inhaled insulin and other systemically targeted macromolecules.

The development of multidose reservoir powder inhalers was pioneered by AstraZeneca with the Turbuhaler™ (27). The design of the delivery system generally enables the efficient aerosolization and dispersion of pure aggregated drug material without excipients. There are more recent examples of multidose reservoir devices that have gained regulatory approval in many countries for the treatment of asthma (31). However, the challenges associated with accurate dose metering and susceptibility to environmental conditions in multidose systems can often cause regulatory dilemma.

Dry Powder Inhalers at various stages of development.

<i>Passive Powder Inhalers</i>	<i>Classification</i>	<i>Dispersion Mechanism</i>
Spinhaler® (Fisons)	Unit Dose	Pierced capsule rotates on impeller – vibratory dispersion (10)
Rotahaler® (GSK)	Unit Dose	Capsule separates with dispersion via plastic grid (11)
Inhalator® (Boehringer Ingelheim)	Unit Dose	Stationary capsule pierced - dispersion via capillary fluidization (8)
Aerosolizer® (Novartis)	Unit Dose	Pierced capsule rotates in chamber-dispersion aided by grid (12)
Solo® (Inhale Therapeutic Systems)	Unit-Dose	Dispersion via turbulent airflow pathway (13)
Orbital® (BrinTech International)	Unit Dose	Dispersion via centrifugal acceleration mechanism (14)
US Patent 6,092,522 (RPR)	Unit Dose	Pierced capsule rotates rapidly within a chamber (15)
US Patent 6,102,035 (Astra)	Unit Dose	Disposable inhaler - airflow pathway entrainment and dispersion (16)
Diskhaler® (GSK)	Multi-Unit Dose	Pierced blister - dispersion via turbulent airflow pathway & grid (17)
Accuhaler® (GSK)	Multi-Unit Dose	Pierced blister - dispersion via turbulent airflow pathway (18)
Inhalator M® (Boehringer- Ingelheim)	Multi-Unit Dose	Stationary capsule pierced - dispersion via capillary fluidization (8)
Flowcaps® (Hovione)	Multi-Unit Dose	Capsule based device - dispersion via turbulent airflow pathway (19)
Spiros® S2 (Elan Corporation)	Multi-Unit Dose	Dispersion via free floating beads and a dosing chamber (20)
Technohaler® (Innovata Biomed)	Multi-Unit Dose	Dispersion via turbulent airflow pathway (21)
US Patent 5,469,843 (3M)	Multi-Unit Dose	Pierced capsule rotates rapidly within a chamber (22)
US Patent 5,724,959 (AEA Technology)	Multi-Unit Dose	Dispersion via impaction and turbulent flow (23)
US Patent 6,182,655 (Jago Research)	Multi-Unit Dose	Dispersion via turbulent airflow pathway (24)
US Patent 6,209,538 (Innova. Devices)	Multi-Unit Dose	Airflow diversion around powder until optimal flow rate achieved (25)
US Patent 6,237,591 (Dura)	Multi-Unit Dose	Turbine powdered inhaler with impeller (26)
Turbuhaler® (AstraZeneca)	Multidose Reservoir	Dispersion via turbulent airflow pathway (27)
Easyhaler® (Orion)	Multidose Reservoir	Dispersion via turbulent airflow pathway (28)
Clickhaler® (Innovata Biomed)	Multidose Reservoir	Dispersion via turbulent airflow pathway (29)
Pulvinal® (Chiesi)	Multidose Reservoir	Dispersion via turbulent airflow pathway (30)
Twisthaler® (Schering Plough)	Multidose Reservoir	Dispersion via turbulent airflow pathway (31)
SkyePharma DPI (SkyePharma)	Multidose Reservoir	Dispersion via turbulent airflow pathway (32)
Taifun® (Leiras)	Multidose Reservoir	Dispersion via turbulent airflow pathway (33)
Novolizer® (Sofotec GmbH)	Multidose Reservoir	Dispersion via turbulent airflow pathway (34)
MAGhaler® (Mundipharma)	Multidose Tablet	Dispersion via turbulent airflow. Formulation present as tablet (8)
US Patent 5,505,196 (Bayer)	Multidose Reservoir	Dispersion via turbulent airflow in a 'swirl chamber' (35)
US Patent 5,699,789	Multidose Reservoir	Dispersion via turbulent airflow pathway (36)
US Patent 5,975,076 (King's College)	Multidose Reservoir	Dispersion via turbulent airflow pathway (37)
<i>Active Powder Inhalers</i>	<i>Classification</i>	<i>Dispersion Mechanism</i>
Inhance PDS® (Inhale)	Unit-Dose	Gas assisted – compressed air disperses powder formulation(38)
Spiros® (Elan Corporation)	Multi-Unit Dose	Electromechanical energy – battery operated impeller (39)
Prohaler® (Valois)	Multi-Unit Dose	Gas – assisted – built in pump provides compressed air (8)
US Patent 5,349,947	Multi-Unit Dose	Explosive blister is crushed between piston + anvil (40)
US Patent 5,388,572 (Tenax)	Multi-Unit Dose	Gas assisted – inhalation activated piston (41)
US Patent 5,875,776 (Vivorx)	Multi-Unit Dose	Gas assisted – electrostatic charger discharges on spacer (42)
US Patent 6,142,146 (Microdose)	Multi-Unit Dose	Electronic circuitry with dispersion via vibration (43)
US Patent 6,237,590 (Delsys)	Multi-Unit Dose	Electrostatic powder dosing coupled with electronic release (44)

FIGURE 1ASmart Particles used in Dry Powder Inhalers (a) PulmoSol™
(Courtesy of Alaris Therapeutic Systems)**FIGURE 1B**Smart Particles used in Dry Powder Inhalers (b) Alrik™
(Courtesy of Alaris Therapeutic Systems)

Novel Formulation Strategies

Optimization and control of particle-particle and particle-inhaler interactions is of critical importance in the development of efficient dry powder inhaler systems. A paradoxical situation exists in powder formulations – drug particles should be < 5 mm aerodynamic diameter to ensure efficient lung deposition, but should also exhibit acceptable flow properties required for accurate dose metering. Thus, micronized powders are often blended with 'coarse' inert carriers e.g. lactose, glucose, or alternatively pelletized as loose agglomerates to improve powder flow (8). Interparticle forces between drug-drug and drug-carrier particles must be sufficient to withstand disruption by general processing techniques, but should allow efficient dispersion of drug, upon the application of a removal force when the patient inhales. Conventional particle formation methods require a secondary milling and micronization stage to produce particles, which will deposit efficiently in the deep lung region. Unfortunately, the resulting particles are highly charged and very cohesive (45). In recent years, the industry has focused significant resources on alternative particle generation technologies, which can be divided into two techniques (1) spray drying (46, 48-69) and, (2) supercritical fluid condensation (45, 70-79) in an effort to produce 'smart' particles and improve DPI efficiency and reproducibility. Particle engineering to produce high purity, chemically stable particles with controlled physico-chemical properties seems to be the direction in which much of the industry is moving towards, driven by a technical need to produce respirable particles of 'unstable' compounds. There is a misconception in the industry that because peptides and proteins are susceptible to enzymatic degradation, they are fragile and cannot withstand size reduction processing, however, there

are reports which demonstrate successful jet milling of such molecules (80).

(1) Particle Engineering Using Spray Drying

Spray drying is recognized as a viable alternative for the production of powders for inhalation (46). Generally spray dried particles are spherical and often hollow, resulting in a powder with a low bulk density in comparison to the starting material. The major drawback of the spray drying process is that metastable, high energy amorphous forms that may crystallize over time and influence product performance are generally created (47). Improved aerosol efficiency can be achieved by co-spray drying with excipients such as sodium chloride (48), human serum albumin (49) or carbohydrates e.g. lactose, mannitol, trehalose or combinations thereof (50-55). Particles of insulin (52), α -1-antitrypsin (56) and β -interferon (57) have all been successfully prepared by co-spray drying with excipients. Co-spray drying with carbohydrates also improves the stability of the peptide or protein and this is the basis of glass stabilization technology (See Figure 1a). Sugars have been used extensively to improve stability in lyophilized protein formulations for injection (58) and thus were an obvious choice as stabilizers in protein powders for inhalation. Proteins are spray dried with 'glass forming' sugars e.g. mannitol, lactose or trehalose, to form an 'amorphous glass state' where the liquid has a very high viscosity. This 'glass state' will remain stable for long periods of time when stored well below the glass transition temperature Tg (temperature when 'glass' \rightarrow 'rubbery' state). Because pharmaceutical products are stored under varying conditions, Tg should preferably be at least 55°C, and thus the excipient or 'glass former' should have a relatively high Tg. As long as the Tg of the powder is higher than any environmental tempera-

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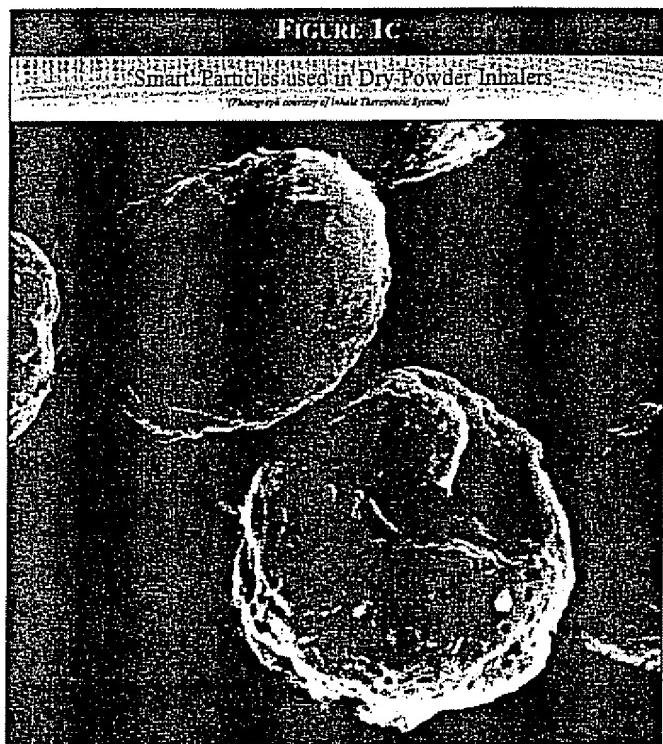


FIGURE 1c

Smart Particles used in Dry Powder Inhalers

(Photograph courtesy of Inhaler Therapeutic Systems)

tures, the powder will remain in a stable 'glass state' (38). Processing of these powders is challenging and is also the subject of extensive patent protection.

Another interesting approach has been the formation of large porous particles (59-65). Large porous particles (comprising poly(lactic-acid-co-glycolic acid) or DL-a-phosphatidylcholine) have been prepared which have geometric diameters in the order of 5-30 μm but because of their low tap density < 0.4g/ml, aerodynamic diameters are in the range 1-5 μm , which is optimal for

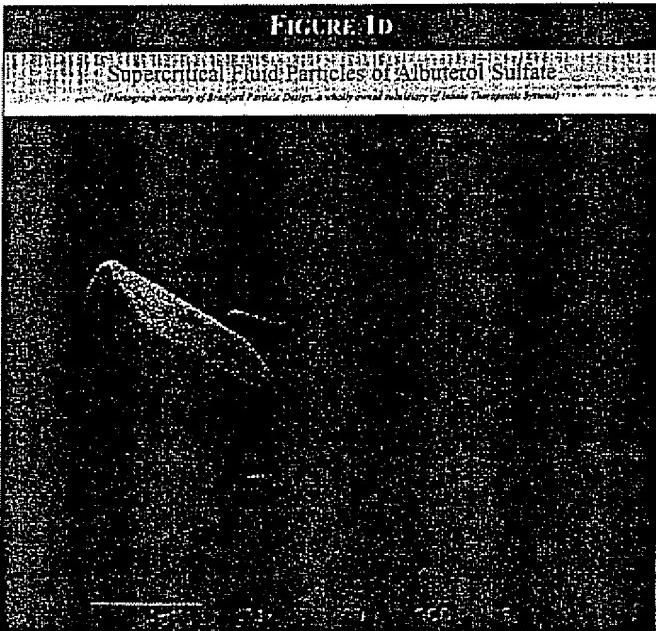


FIGURE 1d

Supercritical Fluid Particles of Albuterol Sulfate

(Photograph courtesy of Inhaler Therapeutic Systems)

lung deposition. Because of the reduced number of surface contacts (See Figure 1b), interparticle interactions are minimized and thus particles are claimed to be less cohesive and demonstrate improved flow and dispersibility. It is further claimed that these large particles are less likely to be phagocytosed than small particles and thus can reside in the lung for relatively long periods of time and offer sustained release options (61). However, proof of concept studies have used very high doses of pulmonary insulin (61) and such claims need further investigation. But, the basic philosophy of large, but light, particles for aerosol delivery shows promise and proof of 'large but light' concept has further been shown to be possible using a spray-freeze drying method (51). Spray freeze drying produced large protein particles with light and porous characteristics which demonstrated improved aerosol performance compared to spray dried particles.

(Figure 1c) provides a further example of novel particle engineering strategies being explored by the aerosol community (67-69). These technologies are based on a novel spray drying process and are hollow and porous particles, which have low particle densities and excellent dispersibility. The porous shell is composed of the drug of interest and 'regulatory friendly' excipients e.g. phosphatidylcholine. These are prepared via a two-stage process. Initially, drug is dissolved in the continuous phase of a fluorocarbon in water emulsion. The resulting emulsion is spray dried with the dispersed fluorocarbon serving as a blowing agent, keeping the particles inflated and creating pores in the drying aerosol droplets.

(2) Particle Engineering using Supercritical Fluid Condensation

'Smart' inhalation particles (Figure 1d) can also be prepared using Super Critical Fluid Condensation methods (45, 70-79). Supercritical fluids (SCFs) are fluids at or above their critical temperature and critical pressure. In this region, SCFs exist as a single phase and possess the solvent power of liquids together with the mass transfer properties of gases (45). Carbon dioxide is the most commonly used SCF because it is non-toxic, non-flammable, inexpensive and has a critical temperature of 31°C that allows operation under ambient conditions. In summary, supercritical fluid processing may resolve many of the limitations associated with conventional particle formation techniques and secondary milling procedures.

In addition, to the novel particle engineering strategies that are being developed, significant efforts are being made to 'breathe life' back into conventional formulations through the management of drug-drug and drug-carrier interactions through the judicious selection of excipients and formulation processing methods. It has long been recognized that drug and carrier properties e.g. size, shape, surface roughness, crystalline state, drug-carrier ratio and the presence of ternary components influence the aerosol dispersion of powder based formulations. There is an extensive literature in this area addressing these issues and Crowder et al. (9) have highlighted succinctly the major issues in their recent article.

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Conclusions

Challenging molecules have stimulated a resurgence of interest in pulmonary drug delivery. Advances in pulmonary drug delivery coupled with the desire to use the lungs as a portal for systemic drug delivery, have identified significant limitations associated with conventional powder formulations and devices. Innovative solutions relating to both particle formation and device design have been discussed in this review. Successful pulmonary delivery requires that powder formulations for inhalation rely upon the integration of drug (and diluent) physicochemical properties (e.g. size, shape, crystallinity) with device performance and characterization, to ensure efficient powder delivery to the deep lung. ■

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